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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,589	01/15/2004	Keizo Koya	3211.1001-001	5403

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
09/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,589	KOYA ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35 and 37-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 1-35 & 37-39 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 6/29/2007 has been received and entered into the application. Accordingly, claims 1, 8, and 17 have been amended and claim 36 has been cancelled.

Applicants' arguments, filed 6/29/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The indication of allowable subject matter in the previous Office Action is hereby withdrawn in view of the Enablement rejection presented herein.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-35 and 37-38 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

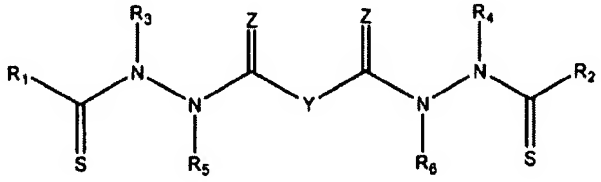
7) the predictability of the art, and

8) the breadth of the claims.

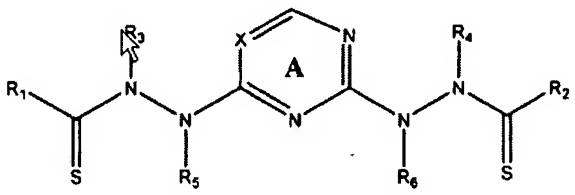
These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to treating a subject having a multi-drug resistant cancer selected from the group consisting of leukemia, uterine sarcoma, and melanoma, comprising administering an effective amount of a compound represented by the following structural formulas:



Claims 1-3, 13-16, 30-33, and 37



Claims 4-6

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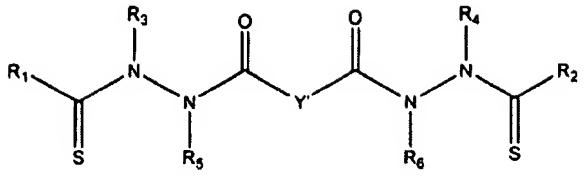
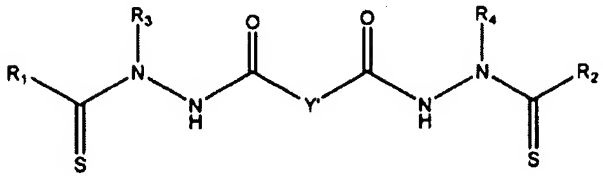
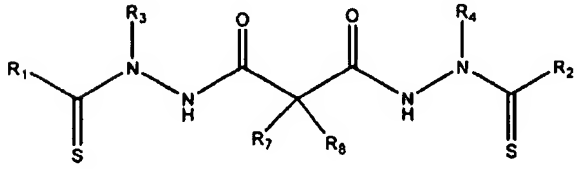
[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".



Claim 7

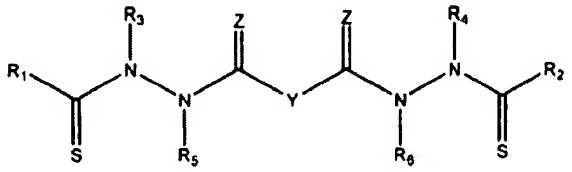


Claims 8-11

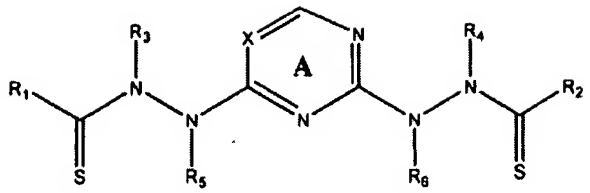


Claim 17

The invention also includes methods of treating a subject having cancer comprising administering a compound having the formulas:



Claims 18-20 and 24-29



Claims 21-23

The substituent definitions of the claimed compounds encompass chemically and biologically distinct groups, including substituted or unsubstituted aliphatic groups or aryl groups (R_1-R_6), substituted or unsubstituted straight chained hydrocarbyl groups (Y), and substituted or unsubstituted aromatic groups (C=Z groups taken together). Further, R_1 and R_3 and/or R_2 and R_4 taken together with the carbon or nitrogen atoms to which they are bonded, can form a non-aromatic heterocyclic ring optionally fused to an aromatic ring.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention

concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art, the examiner cites Sausville *et al.* (Cancer Research, 2006, vol. 66, pages 3351-3354) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Sausville *et al.*, cited for evidentiary purposes, teaches that traditionally explored tumor model systems are insufficient to predict how actual human beings will respond to treatment in the clinic (page 3351, left column). Even when drugs with evidence of anticancer activity in preclinical *in vivo* models are given their maximum tolerated dose in humans, they frequently fail to produce useful activity in humans (*id.*). Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

2. The breadth of the claims

The claims are extremely broad insofar as they disclose the general treatment of multi-drug resistant leukemias, uterine sarcomas, or melanomas and the treatment of any cancer by administering to a subject a compound as defined in the claims. It is noted that the claimed chemical formulas encompass millions of possible compounds.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all of the various cancers claimed, particularly in humans.

The direction concerning treating cancer is found in the specification at pages 79-94, which provides *in vitro* cellular assays and *in vivo* assays for determining the cell growth inhibitory effect of the claimed compounds. In this regard, compound **1** (page 80) was shown to inhibit the growth of a myeloid leukemia cell line (HL-60), a uterine sarcoma cell line (MES-SA), and a melanoma cell line (Bowes/OV2) *in vitro*. Compounds **2-18** were shown to inhibit the growth of the multi-drug resistant uterine sarcoma cell line, MES-SA/DX5, *in vitro* (Table 2). It is noted that all of these compounds have similar substitutions (*e.g.*, in all cases, Y is CH_2 and R_5 and R_6 are H, and in the majority of compounds R_1 and R_2 are unsubstituted or substituted phenyl and R_3 and R_4 are methyl, ethyl, or phenyl). None of the above compounds have C=Z taken together to form a substituted or unsubstituted aromatic group, or R_2 and R_4

taken together with the carbon and nitrogen to which they are bonded forming a non-aromatic heterocyclic ring optionally fused to an aromatic ring. Further, none of the above compounds have R_5 and/or R_6 as an unsubstituted aliphatic group, a substituted aliphatic group or a substituted or unsubstituted aryl group. A compound structurally similar to compound **1** (compound **16**) was shown to have *in vivo* activity against a multi-drug resistant uterine carcinoma in nude mice at a dose of 15 mg/kg (Example 17). Compound **1** also was shown to inhibit leukemia cell growth *in vitro* (Example 19) and *in vivo* (Example 20). Thus, out of the millions of possible compounds encompassed by the claims, only two structurally related compounds (compounds **1** and **16**) were tested *in vivo* (against uterine sarcoma and leukemia) and 16 additional compounds were tested *in vitro* against one cell line (MES/DX5 cells).

Applicants describe formulations at pages 22-23. Doses required to practice their invention are also described at pages 22-23. In this regard, Applicants disclose that "an effective amount" of the claimed compounds is the quantity of compound in which "a beneficial clinical outcome is achieved when the compound is administered to a subject with a cancer" (page 22, lines 26-28). A 10,000-fold range of doses is recommended (*e.g.*, 1 mg to 10 g/mm^2 per day)[2].

Since only 18 structurally related compounds of the invention have been shown to be effective against MES-SA/DX5 cells (a multi-drug resistant uterine sarcoma cell line) *in vitro* (Table 2) and only two structurally related compounds have shown efficacy *in vivo*, how is the skilled physician to know what dose to administer to a subject for each of the pathologically different cancers and structurally diverse compounds encompassed by the claims? There are no

[2] It is noted that the "mm^2" appears to be a typo as m^2 is traditionally used to refer to doses. For example, an average human has a surface area of about 2 m^2.

guidelines for determining the doses needed to treat a carcinoma *vs.* a myeloid disorder *vs.* adenoma *vs.* leukemia. Are the identical doses to be used for treating these unrelated cancers? There are both *in vitro* cellular assays and *in vivo* assays described in pages 79-94, but it is unclear if these assays correlate to the clinical treatment of all of the cancers encompassed by the claims. For example, there is no working example of treatment of any cancer in a human subject. Further, it is not apparent that the eighteen compounds that Applicants tested are representative of the millions of possible structurally diverse compounds encompassed by the claims.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the full scope of the instantly claimed genera of compounds could be predictably used as a treatment for all cancerous cell growth as inferred in the claims and contemplated by the specification. While some claims are limited to the treatment of multi-drug resistant leukemia, uterine sarcoma, and melanoma, it is not seen that the experimental results presented in the specification are commensurate in scope with the claims, which encompass millions of possible compounds.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because 17 compounds of the invention inhibit uterine sarcoma cell proliferation *in vitro* and two structurally related compounds have shown activity against uterine sarcoma and leukemia *in vivo*, the millions of possible compounds encompassed by the claims must therefore, *a priori*, be useful in the treatment of cancerous cell growth. However, the claims encompass a multitude of compounds (literally millions) having a plethora of chemically and biologically distinct substituents. Accordingly, the evidence of biological activity presented in the specification is not seen as commensurate in scope with the patent protection sought by Applicants. Further, it would take undue experimentation to determine exactly what compounds encompassed by the claims will have efficacy against any given cancer in a subject.

In this regard, the law requires that disclosure in an application shall inform those skilled in the art how to use Applicant's invention, not how to find out how to use for themselves. Applicants say that their invention is in the discovery of a novel class of anticancer compounds. They are not claiming the compounds *per se*. There are three consecutive paragraphs (pages 22-23) of the specification and one specific example (page 93, Example 20) collectively relating to dosage and administration techniques which may be summarized as saying that the compounds can be administered in all the usual ways, as solids, solutions, and suspensions; in capsules, tablets, or suspensions; to be administered orally, parenterally, by inhalation, or rectally; and the carrier may include any suitable pharmaceutically acceptable carrier. Whatever the nature of the dosage unit, it may be administered in a range of 1 mg/mm^2 [m^2] per day to about 10 grams/mm^2 [m^2] per day. The "effective dose" as instantly claimed appears to mean that somewhere in the above dose range, an anticancer effect in a subject will be achieved. However, Applicants do not

say at what point in the process of administering to a patient, say a 10 mg capsule, an anticancer effect may be expected in the course of proceeding at some unspecified intervals toward a possible 500th capsule for the day (*i.e.*, a total of 5 grams/day for an average human). Nor do the Applicants suggest whether in might be better to start off with a 10 mg capsule, a 50 mg tablet or a 150 mg bolus injection.

This uncertainty, particularly when coupled to the fact that the claims encompass millions of possible compounds, which, in turn, is coupled to the fact that the subject being treated is not necessarily a human being, amounts to a failure to comply with the requirements of 35 U.S.C. 112, 1st Paragraph. In effect, Applicants have said to those skilled in the art: Here is a group of new compounds, some of which have been shown by us to have anticancer activity *in vitro* against three cell lines and two of which have shown anticancer activity *in vivo* against leukemia and uterine sarcoma; you can put any of them up in convenient dosage units and you can try them out on human patients or animal subjects as you wish and somewhere along the line, for any given compound in any given cancer, from a dose of 1 mg/m^2 per day to 10 grams/m^2 per day, you will probably achieve an anticancer effect in a subject.

In other words, those skilled in the art, by investigations along the above lines, and by a great amount of work, can eventually find out how to use the Applicants' invention to treat cancers in subjects by administering one of the millions of compounds encompassed by the claims. It is evident that a very small percentage of the claimed compounds were actually synthesized and tested by Applicants and the two compounds tested *in vivo* were closely related in structure. In other words, the structure activity relationship demonstrated in the examples is limited to a very small sub-genus of compounds.

Determining if any particular claimed compound would treat any particular cancerous disease state would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants. Further, as noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

September 14, 2007

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER